Supplementary Online Content

Torbahn G, Hofmann H, Rücker G, et al. Efficacy and safety of antibiotic therapy in early cutaneous Lyme borreliosis: a network meta-analysis. *JAMA Dermatol*. Published online October 3, 2018. doi:10.1001/jamadermatol.2018.3186

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definition of Treatment Response and Assessment of Treatment Response in the Individual Studies

Reference	Definition of treatment response[a]	Assessment of treatment response[a]
Aberer 2006	"**Treatment failure** was defined as persistence or recurrence of EM or concomitant symptoms, or the development of new manifestations in the 12-month follow-up period."	"Patients were investigated using a standardized questionnaire (…)."
Barsic 2000	"(i) **success** – resolution of EM rash and other clinical signs and symptoms in a period of 14 days after the start of therapy and absence of major manifestations during follow-up period; (ii) **improvement** – incomplete resolution of EM and/or incomplete resolution of other clinical signs and symptoms of early LD in a period of 14 days after the start of therapy with further improvement or complete resolution during follow-up; (iii) **failure** – no improvement in EM rash or other clinical signs and symptoms; recurrence or new onset of EM and other signs and symptoms; new onset of the major clinical manifestations of LD during follow-up period; withdrawal because of adverse drug event which necessitates change of antimicrobial therapy."	"The response to therapy was evaluated on the basis of the EM remission and eventual subsequent appearance of major manifestations (carditis, arthritis, radiculopathy and meningitis) (…)."
Breier 1996	"Signs or symptoms of late Lyme borreliosis after 1 year."	"In all patients a physical examination was performed (…)."
Cerar 2010	"**Complete response** at 2, 6, and 12 months post-enrollment was defined as continued absence of objective manifestations of Lyme disease, with return to pre-LD health status. **Partial response** was defined as the presence of new or increased symptoms without an objective manifestation. **Failure** was defined as the occurrence of objective manifestations of LD or persistence of B. burgdorferi sensu lato in skin at the site of the previous EM."	"The skin biopsy sample was cultured in modified Kelly-Pettenkofer medium. (…) patients were asked about the presence of subjective symptoms (…)."
Dattwyler 1990	"(…) **Major late features** were defined as active CNS infection, meningitis, or meningoencephalitis (severe headache, stiff neck on physical examination, and cerebral spinal fluid pleocytosis); myocarditis (atrioventricular nodal block or left ventricular dysfunction); or recurrent attacks of arthritis (pain on movement and swelling of at least one joint, as judged by physical examination). **Minor late features** were cranial neuropathy (without evidence of active CNS infection); brief arthritis (one episode for <2 weeks); severe unremitting fatigue (interfering with daily activities); or arthralgia (joint pain without abnormal physical findings). Patients with no signs or symptoms other than mild self-limited fatigue were considered to have no late disease."	"The clinical features of LD were described to each patient and they were advised to notify the clinic immediately if signs or symptoms of progression developed."

Reference	Definition of treatment response	Assessment of treatment response
Eliassen 2018	Data not presented in publication but requested by the study author: (1) **Complete response**: remission of EM and accompanied symptoms; (2) **Partial response**: remission of EM but presence of "minor symptoms";. (3) **Failure**: presence of EM and/or dissemination of Borrelia/ development.	"(…) self-reported questionnaire, by which patients assessed whether they experienced symptoms that could possibly be caused by disseminated LB. (…)."
Hansen 1992	Not evaluated in NMA	Not evaluated in NMA
Luft 1996	"(1) **Complete response**: complete clearance of EM and all objective signs and greater than 75% relief of presenting symptoms. (2) **Partial response**: 1) complete clearance of EM with persistent signs and 50% to 75% relief of symptoms or 2) persistent EM with complete clearance of signs and greater than 75% relief of symptoms. (3). **Treatment failure**: 1) persistent EM, persistent signs, and less than 50% relief of symptoms or 2) development of new signs and symptoms of disease before the examination on day 20."	"Patients were evaluated by a physician (…). Subjective symptom scores for 11 key symptoms (…) were recorded on a visual analog scale at each evaluation. (…) serologic testing (…) and liver function tests. Electrocardiography (…)."
Luger 1995	"The clinical response (…) at 1 month posttreatment (…): (i) **success** (resolution of EM rash and other clinical signs and symptoms (…), (ii) **improvement** (resolution of erythema rash but incomplete resolution of any other clinical signs and symptoms of early LD by the posttreatment visit on days 1 to 5, with further improvement or complete resolution by the 1-month posttreatment follow-up visit), (iii) **failure** (no improvement in EM rash or other clinical signs and symptoms of early LD by the posttreatment visit on days 1 to 5) (…). The clinical response of each patient at 1 year posttreatment was categorized as follows: (i) **success** (no signs or symptoms of late LD [arthralgia, fatigue, arthritis, carditis, neurologic disease] (…)), (ii) **improvement** (some signs or symptoms consistent with late LD but no objective evidence of active disease), or (iii) **failure** (signs or symptoms of late LD, including seropositivity for antibodies to B. burgdorferi)."	"A complete medical history and physical examination were done (…). (…) blood count, clinical chemistry testing, electrocardiographic evaluation, and urinalysis (…). (…) serologic assessment."
Massarotti 1992	**Complete response**: Symptoms of LD resolved within 3 to 10 days. **Partial response**: additional treatment for 10 days. **Treatment failure**: additional treatment for 10 days and development of subsequent symptoms (facial palsy, difficulty concentrating, memory loss, fatigue, radicular pain).	"Observation of this rash by a study physician was sufficient for diagnosis."
Nadelmann 1992	See Luger 1995	See Luger 1995
Steere 1983	Not evaluated in NMA	Not evaluated in NMA

Reference	Definition of treatment response	Assessment of treatment response
Strle 1992	"Patients were asked to record the time when their skin lesions and co-existing local symptoms began to clear and the time of **complete resolution**. In the event of an exacerbation or development of new symptoms, they were asked to return to the clinic earlier than specified. (…). **Late manifestations** of LB were identified as major or minor according to the criteria of Steere et al. (1983). However, in the present study even a short attack of arthritis was considered a major manifestation, in contrast to Steere who included even brief episodes of arthritis amongst the minor manifestations."	"(…) evaluation included a medical history, physical examination, basic haematological and biochemical investigations, serological tests, urinalysis and electrocardiography."
Strle 1993	"**Late (consecutive) manifestations** of Lyme borreliosis were interpreted as major or minor according to Steere et al. with the exception of arthritis: in the present study even a short attack of arthritis was recognized as a major manifestation (in Steere's study brief arthritis was included among minor manifestations)."	"(…) information about the course of the illness were acquired by questionnaires. (…) At each visit, the clinical history was recorded and a physical examination was carried out. The patients were asked to keep a record of signs and symptoms, including the day of disappearance of their skin lesions."
Stupica 2012	"A **complete response** to treatment was defined as resolution of EM (the interval was calculated as the number of days from starting antibiotic treatment until EM could no longer be seen in daylight at room temperature), with return to pre-Lyme borreliosis health status. **Partial response** was defined as either incomplete resolution of EM or the presence of NOIS. **Complete response** at 2, 6, and 12 months after enrollment and at the last evaluable visit was defined as continued absence of any manifestations of Lyme borreliosis, with return to pre-Lyme borreliosis health status. **Partial response** was defined as the presence of NOIS. **Failure** was defined as the occurrence of new objective manifestations of Lyme borreliosis or the persistence of Borrelia burgdorferi sensu lato in skin at the site of the previous EM."	"(…) patients were examined and asked about the presence of any health-related difficulties that had newly developed or worsened since the onset of EM. If such symptoms had no other medical explanation, they were regarded as new or increased symptoms. (…) patients were asked to complete a written questionnaire asking whether they had had any of 14 non-specific symptoms (…)."

CNS: Central nervous system. EM: Erythema migrans; LB: Lyme borreliosis; LD: Lyme disease; NMA: Network Meta-analyses. NOIS: New or increased symptoms.
[a] Text in "quotation marks" indicates that the same wording is used as in the primary study.

eTable 2. Study Characteristics

Reference	Setting	Recruitment	Duration of follow-up (mos)	N patients	Age (years)	Females (%)	Patients with MEM (%)	Intervention (agent, dose, duration)
Aberer 2006	Outpatients, multicenter, Austria	1997 - 2001	12	102	50.3±16	53.9	-	Penicillin V (4.5 mio IU, 20 days)
								Penicillin V (4.5 mio IU, 14 days)
Barsic 2000	Outpatients, multicenter, Croatia	-	12	88	44.8	55.7	11.4	Azithromycin (500 mg/d, 5 days)
								Doxycycline (200 mg/d, 14 days)
Breier 1996	Outpatients, monocentric, Austria	04/93-10/93	12	60	43 (19-80)	58.3	-	Penicillin V (4.5 mio IU, 21 days)
								Minocycline (200 mg/d, 21 days)
Cerar 2010	Outpatients, monocentric, Slovenia	06/06-09/06	12	285	52.8 (17-85)	56.5	0	Doxycycline (200 mg/d, 15 days)
								Cefuroxime axetil (1000 mg/d, 15 days)
Dattwyler 1990	Outpatients, monocentric, US	06/88-08/89	6	75	37.5	44.0	14.7	Amoxicillin (1500 mg/d, 21 days) + Probenecid (1500 mg/d, 21 days)
								Doxycycline (200mg/d, 21 days)
Eliassen 2018	Outpatients, multicenter, Norway	06/11-11/13	24	188	55.7 (18-85)	60.0	0	Penicillin V (4.2 mio IU/d, 14 days)
								Amoxicillin (1500 mg/d, 14 days)
								Doxycycline (200 mg/d, 14 days)
Hansen 1992	Outpatients, multicenter, Denmark and Sweden	1989	3	100	>17	-	-	Roxithromycin (350 mg/d, 10 days)
								Penicillin V (2000mg/d, 10 days)
Luft 1996	Outpatients, multicenter, US	06/90-10/91	6	246	42.7	42.9	17.5	Azithromycin (500 mg/d, 7 days)
								Amoxicillin (1500 mg/d, 20 days)
Luger 1995	Outpatients, multicenter, US	05/90-11/90	12	232	46.0	38	13.8	Cefuroxime axetil (1000 mg/d, 20 days)
								Doxycycline (300 mg/d, 20 days)
Massarotti 1992	Outpatients, multicenter, US	-	6	81	45.0±14	47.4	-	Amoxicillin (1500 mg/d, 10 days) + Probenecid (1500 mg/d, 10 days)
								Azithromycin (250 mg/d, 5 days)
								Doxycycline (200 mg/d, 10 days)
Nadelmann 1992	Outpatients, multicenter, US	06/89-09/89	12	123	44.8±15.6	43.9	17.9	Cefuroxime axetil (1000 mg/d, 20 days)
								Doxycycline (300 mg/d, 20 days)
Steere 1983	Outpatients, monocentric, US	1980 -1982		112	36.6±15.1	50.9	-	Penicillin V (1000 mg/d, 10 days)
								Erythromycin (1000 mg/d, 10 days)

			1-6 days after therapy					Tetracycline (1000 mg/d, 10 days)
				49	38.1±13.0	42.9		Tetracycline (1000 mg/d, 10 days): Tetracycline (1000 mg/d, 20 days)
Reference	**Setting**	**Recruitment period**	**Duration of follow-up (mos)**	**N patients**	**Age (years)**	**Females (%)**	**Patients with MEM (%)**	**Intervention (agent, dose, duration)**
Strle 1992	Outpatients, monocentric, Slovenia	09/88-12/88	24	68	39.9±12.2	58.7	9.4	Doxycycline (200 mg/d, 14 days)
								Penicillin V (3 mio IU/d, 14 days)
								Azithromycin (250 mg/d, 10 days)
Strle 1993	Outpatients, monocentric, Slovenia	1990-1991	12	107[a]	43.7±12.6	46.7	10.3	Doxycycline (200mg/d, 14 days)
								Azithromycin (500 mg/d, 5 days)
Stupica 2012	Outpatients, monocentric, Slovenia	06/09-10/09	12	225	52.4 (38-62)	55.6	0	Doxycycline (200 mg/d, 15 days)
								Doxycycline (200 mg/d, 10 days)
Stupica 2015	Outpatients, monocentric, Slovenia	06/10-12/10	12	121	54.0 (43-61)	41.3	0	Cefuroxime axetil (1000 mg/d, 15 days)
								Amoxicillin (1500 mg/d, 15 days)
Weber 1990	Outpatients, monocentric, Germany	07/87-12/88	3	73	45.5±14.5	54.8	-	Ceftriaxone (1 g/d, 5 days)
								Penicillin V (3 mio IU/d, 12 days)
Weber 1993	Outpatients, multicenter, Germany	1989-1991	17[b]	66	46.0 (19-74)	56.9	18.5	Azithromycin (500 mg/d, 10 days)
								Penicillin V[c] (3 mio IU/d, 10 days)
Wormser 2003	Outpatients, monocentric, US	1992 -1994	30	180	44.0±13.5	35.6	-	Ceftriaxone (2 g/d, 1 day) + Doxycycline (200 mg/d, 10 days)
								Doxycycline (200 mg/d, 10 days)
								Doxycycline (200 mg/d, 20 days)

g/d: gram per day; IU: international unit; LD: lyme disease; MEM: multiple erythema migrans; mio: millions; mos: months; US: United States.
[a] 389 patients participated but only 107 with skin culture were analysed and reported; [b] Further follow-up time points (however, not all patients took part): azithromycin 18 (3-32) months and penicillin 16 (3-29) months; [c] Phenoxymethyl penicillin.

eTable 3. Summary of Findings Table: Different Treatment Regimens.[a]

Reference	Intervention	Comparison	N, Patients	Responder (≥12 months)		Failures (≥12 months)		Neuroborreliosis (≥12 months)		Disseminated EM (≥12 months)		Any adverse events[b]	
				I	C	I	C	I	C	I	C	I	C
Barsic 2000	Azithromycin 500 mg/d for 5 days	Doxycycline 200 mg/d for 14/15 days	88	na	na	na	na	na	na	na	na	5/47	5/35
Cerar 2010	Cefuroxime axetil 1000 mg/d for 14/15 days		285	114/140	114/145	0/140	2/140	0/140	0/145	0/140	1/145	23/140	22/145
Eliassen 2018	Penicillin V 4.2 mio IU/d for 14 days		188	56/56	68/68	0/56	0/68	0/56	0/68	0/56	0/68	24/55	29/67
	Amoxicillin 1500 mg/d for 14 days			64/64		0/64		0/64		0/64		33/64	
Strle 1992	Penicillin V 3 mio IU/d for		68	19/23	21/23	2/23	2/23	1/23	1/23	0/23	0/23	5/21	12/23

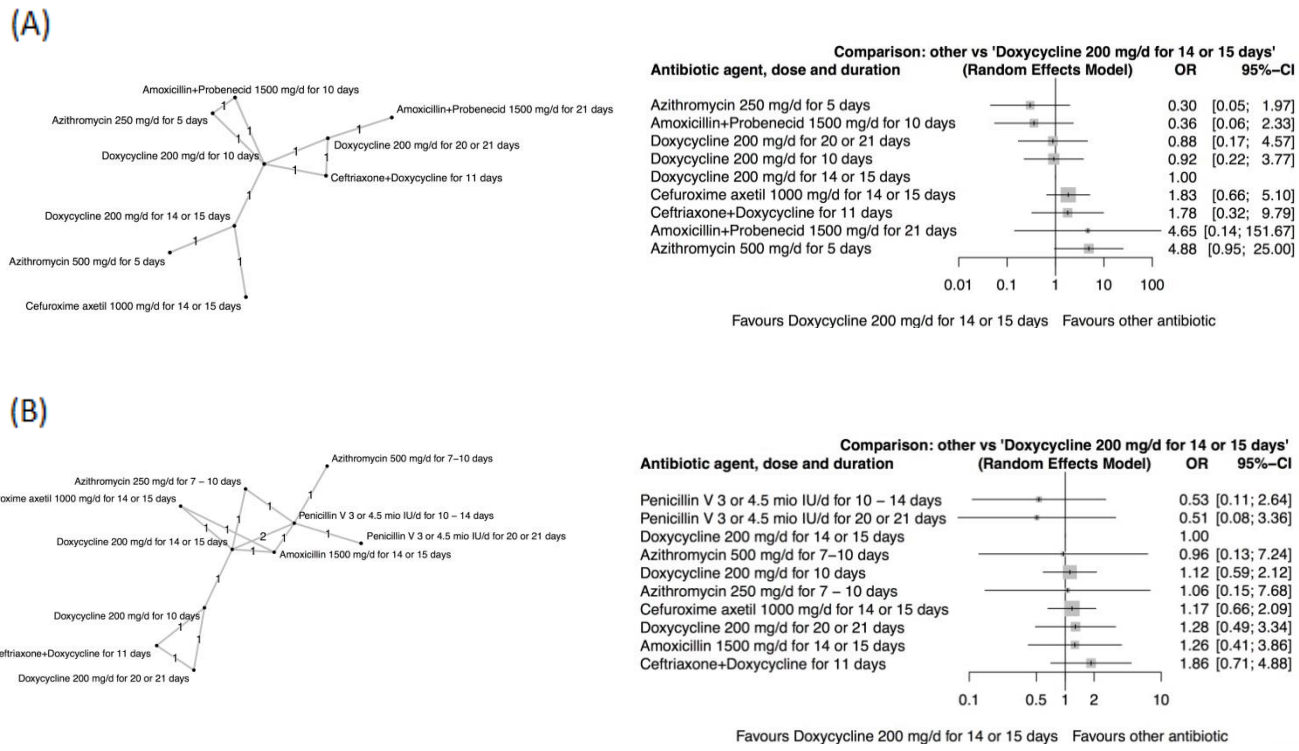
	14 days												
	Azithromycin 250 mg/d for 10 days			20/22		0/22		0/22	0/22	0/22	0/22	8/20	
Strle 1993	Azithromycin 500 mg/d for 5 days		107	na	na	na	na	na	na	na	na	12/55	27/52
Stupica 2012	Doxycycline 200 mg/d for 10 days		225	86/108	91/117	0/108	0/117	0/108	0/117	0/108	0/117	0/108	7/117
Massarotti 1992	Amoxicillin 1500 mg/d for 10 days + Probenecid 1500 mg/d for 10 days	Doxycycline 200 mg/d for 10 days	81	na	na	na	na	na	na	na	na	8/19	2/22
	Azithromycin 250 mg/d for 5 days			na	na	na	na	na	na	na	na	3/16	

Wormser 2003	Ceftriaxone 2 g/d for 1 day + Doxycycline 200 mg/d for 10 days		180	37/60	30/61	0/60	1/61	0/60	1[c]/61	0/60	0/61	37/60	27/61
	Doxycycline 200 mg/d for 20 days			31/59		0/59		0/59		0/59		25/59	
Dattwyler 1990	Amoxicillin 1500 mg/d for 21 days + Probenecid 1500 mg/d for 21 days	Doxycycline 200 mg/d for 21 days	75	na	na	na	na	na	na	na	na	8/38	5/37
Luger 1995	Cefuroxime axetil 1000 mg/d for 20 days	Doxycycline 300 mg/d for 21 days	232	na	na	na	na	na	na	na	na	37/119	50/113
Nadelmann 1992	Cefuroxime axetil 1000		123	na	na	na	na	na	na	na	na	37/63	24/60

	mg/d for 20 days												

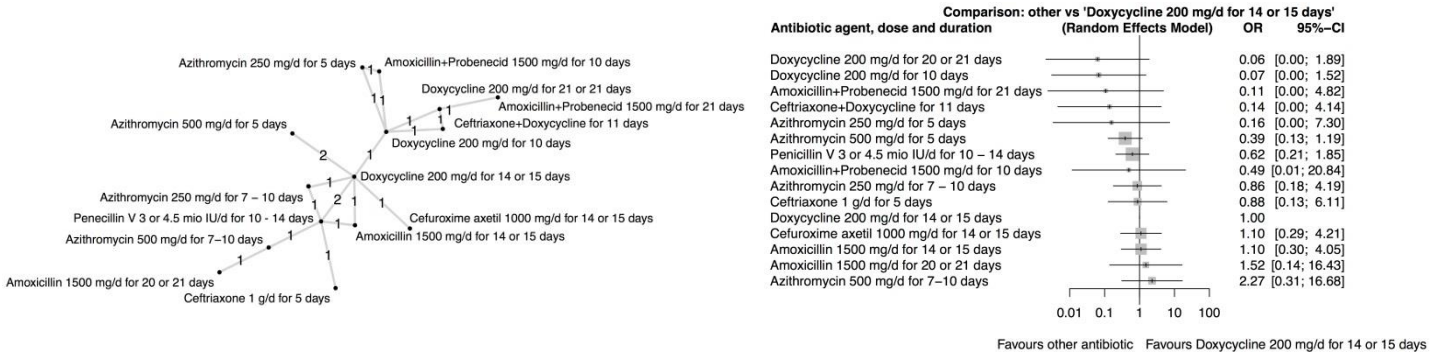
C: Comparison treatment; I: Intervention; na: not available.
[a] Studies comparing any antibiotic treatment regimen with reference to doxycline (n=11 studies); [b] Any adverse events occurring at any time during the antibiotic treatment; [c] Pleocytosis.

eFigure 1. Outcome: Response to Treatment



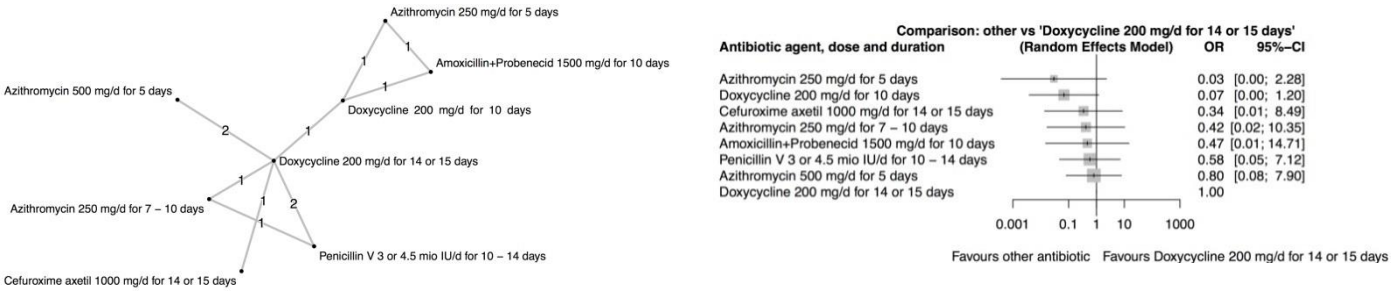
eFigure 1. Network graph and forest plot for the outcome response to treatment for different regimens (dosage and/or duration). **(A)** ≤ 2 months after start of treatment: 6 RCTs, 9 antibiotic treatment modalities (nodes), 934 patients. **(B)** ≥ 12 months after start of treatment: 8 RCTs, 10 treatment modalities (nodes), 1235 patients. Doxycycline (200 mg/d, 14-15 days) was the reference treatment.

eFigure 2. Outcome: Any Reported Adverse Events



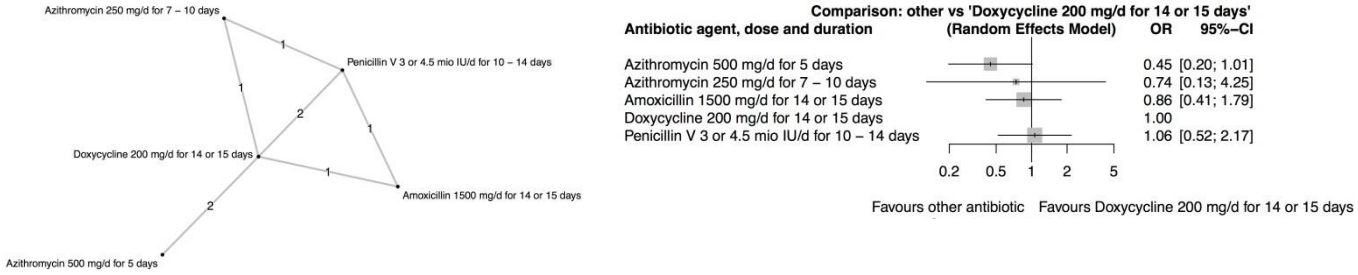
eFigure 2. Network graph and forest plot for the outcome any reported adverse events for different regimens (dosage and/or duration). Doxycycline (200 mg/d, 14-15 days) was the reference treatment: 12 studies, 15 antibiotic treatment modalities (nodes), 1624 patients.

eFigure 3. Outcome: Any skin-Related Adverse Events



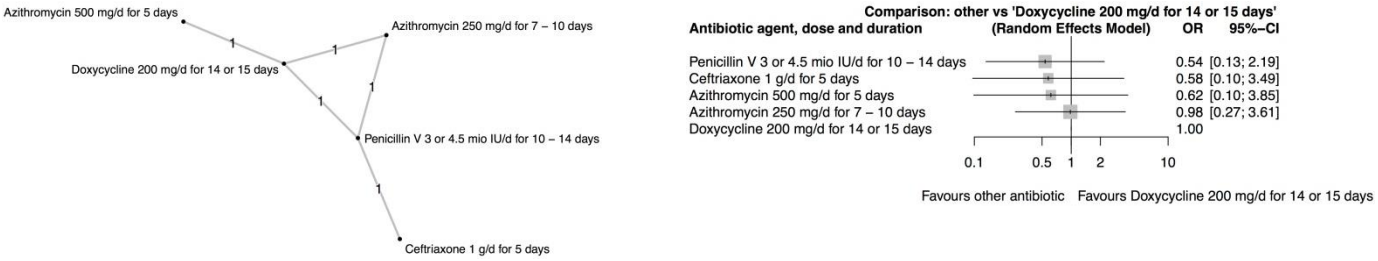
eFigure 3. Network graph and forest plot for the outcome any skin-related adverse events for different regimens (dosage and/or duration): 7 studies, 8 antibiotic treatment modalities (nodes), 1006 patients. Doxycycline (200 mg/d, 14-15 days) was the reference treatment.

eFigure 4. Outcome: Any Gastrointestinal Adverse Events



eFigure 4. Network graph and forest plot for the outcome gastrointestinal-related adverse events for different regimens (dosage and/or duration): 4 studies, 5 antibiotic treatment modalities (nodes), 439 patients. Doxycycline (200 mg/d, 14-15 days) was the reference treatment.

eFigure 5. Outcome: Jarisch-Herxheimer–Like Reactions



eFigure 5. Network graph and forest plot for the outcome Jarisch-Herxheimer-like reactions for different regimens (dosage and/or duration): 3 studies, 5 antibiotic treatment modalities (nodes), 244 patients. Doxycycline (200 mg/d, 14-15 days) was the reference treatment.

eAppendix 1. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.[1]

Section/Topic	Item	Checklist Item	Reported on Page
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*[a]	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**3,4**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**5**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**7**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**7**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**7**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**7 and eMethods 3**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**7**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from	**7-8**

		investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**8**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**9,10**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**8,9**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**9,10**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: *Handling of multi-arm trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit.*	**9,10**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**9,10**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**8,9**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**9,10 and eMethods 2**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**11 and Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 3**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**12-14**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**11 and eTable 1/2**

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**11,12 and Figure 2**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Table 1 eTable 3**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**12-15 and Figure 3 and eFigures 1-5**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**12-15 and Table 1**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**Table 1**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**Not applicable**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**16**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**17**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**18/19**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**20**

PICOS; population, intervention, comparators, outcomes, study design.
[a] Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

Reference

1. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.

eAppendix 2. Differences Between Protocol and Review

The review has a published protocol.[1] A change in authors occurred: Gerta Ruecker and Karin Bischoff joined the review team. Thereby, Gerta Ruecker replaced Harriet Sommer as statistician and Karin Bischoff replaced Roman Allert as second reviewer carrying out data extraction. The original plan was to perform a systematic review including pairwise meta-analyses. The high number of identified randomized studies comparing different antibiotic agents and treatment modalities against each other, however, proposed a more sophisticated analysis. Therefore, we conducted network meta-analyses. This approach enabled us to synthesize information of different studies addressing the same outcomes, but involving different interventions. We had planned sensitivity analyses to determine the impact of bias by exclusion of studies with high or unclear Risk of Bias. Such analyses, however, were not conducted, because most identified studies showed either a high or unclear risk of bias.

Reference:

1. Torbahn G, Hofmann H, Allert R, et al. Efficacy and safety of pharmacological agents in the treatment of erythema migrans in early Lyme borreliosis-systematic review protocol. *Syst Rev.* 2016;5:73.

eAppendix 3. Search Strategy Database(s) in MEDLINE(R) (via Ovid on 2015-11-24)

1. exp Lyme Disease/
2. lyme*.mp.
3. exp Borrelia/
4. borreli*.mp.
5. tick*.mp.
6. (erythem* adj2 migran*).mp.
7. dermat*.mp.
8. cutan*.mp.
9. exp Erythema/
10. erythem*.mp.
11. exp Skin Diseases, Bacterial/
12. skin diseas*.mp.
13. acroderm* chron* atrophi*.mp.
14. mult* erythem* migran*.mp.
15. Scleroderma, Localized/
16. local* slcero*.mp.
17. circ* sclero*.mp.
18. morphea.mp.
19. Pseudolymphoma/
20. pseudolymphom*.mp.
21. lymphocytom*.mp.
22. (cutan* adj2 lymphocyt*).mp.
23. Lichen sclerosus/
24. Lichen sclero*.mp.
25. atroph*.mp.
26. aneto*.mp.
27. granuloma*.mp.
28. neuroborreli*.mp.
29. arthritis.mp.
30. carditis.mp.
31. early locali*.mp.
32. (early adj2 lyme*).mp.
33. (early adj2 borrel*).mp.
34. acute lyme*.mp.
35. (acute adj2 borrel*).mp.
36. early dissem*.mp.
37. late dissem*.mp.
38. late lyme*.mp.
39. (late adj2 borrel*).mp.
40. (dissem* adj2 borrel*).mp.
41. (chron* adj2 borrel*).mp.
42. chron* lyme*.mp.
43. (subacute adj2 borrel*).mp.
44. subacute lyme*.mp.
45. (refractory adj2 borrel*).mp.
46. refractory lyme*.mp.
47. or/1-5
48. or/6-12
49. or/13-30
50. or/31-46
51. 48 or 50
52. 49 or 50
53. 47 and 51
54. 47 and 52
55. 53 or 54